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WATER, CHLORIDE AND POTASSIUM EXCHANGES IN ISOLATED BLOOD-PERFUSED DOG LUNGS

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The work described in this paper is the continuation of an investigation begun by Daly, Eggleton, Elsden & Hebb (1946) into the blood changes associated with the occurrence of oedema in isolated perfused dog lungs; and to what extent such changes may be used to distinguish oedema which is of unknown or 'spontaneous' origin from that which is due to phosgene. Most of the changes then found to be associated with oedema could be ascribed solely to haemo-concentration; and of all which had been investigated the plasma water and Cl values seemed the most useful in determining the onset of oedema from whatever cause. There was no evidence, however, that phosgene produced any specific changes in the blood.

From subsequent observations it appeared likely that the blood and plasma K concentration might be specifically affected by phosgene. Changes in potassium concentration in the perfusate in normal and phosgene-poisoned isolated dog lungs have been investigated and, in addition, a further analysis has been made of the alterations in plasma volume and Cl which are associated with oedema.

METHODS

The experiments were performed on dog lungs, isolated and perfused with heparinized blood at constant volume inflow using negative pressure ventilation (extra-pulmonary pressure varying from −0·4 to *c.* −9 cm. water at a rate of 12½/min.). Two independent preparations were obtained in each experiment by perfusing the right and left lungs separately and in parallel (Daly, Hebb & Petrovskaia, 1941; Hebb & Nimmo-Smith, 1946).

One preparation was treated with phosgene some 1–2 hr. after beginning perfusion; the other was used as a control. In some experiments a cross-circulation was established between the test and control lungs for limited periods before and/or during gassing.

The pulmonary arterial pressure and tidal air were recorded continuously by kymograph, using recorders of the type described by Daly (1938). The venous reservoir volume of each system was noted at 10 or 15 min. intervals. Each reservoir was calibrated and readings were made directly (accuracy ±3 ml.).

Alterations in the circulating volume of blood due to extravascular losses of water by evaporation, to lung blood volume changes, and to extravascular tissue uptake of fluid, were calculated by methods already described (Daly *et al.* 1946). Methods for blood analyses were those used earlier (Hebb & Nimmo-Smith, 1946).

Administration of phosgene. Each lung was connected by its bronchial cannula and communicating tubing (wide-bore glass and rubber tubing) to a small spirometer (210 ml. capacity), the whole system being closed and having a capacity of 300–400 ml.

Gas was injected into the airway through a glass capillary tube let into the bronchial cannula near its opening into the lung. The other end of the capillary tube was on the outside of the respiratory chamber and was connected to a 3-way glass tap which in turn communicated with a 1 ml. all-glass syringe containing the gas. A second 20 ml. syringe was attached to the third outlet of the tap, and this was used as a reservoir from which the smaller syringe could be recharged when required. (See Fig. 1.)

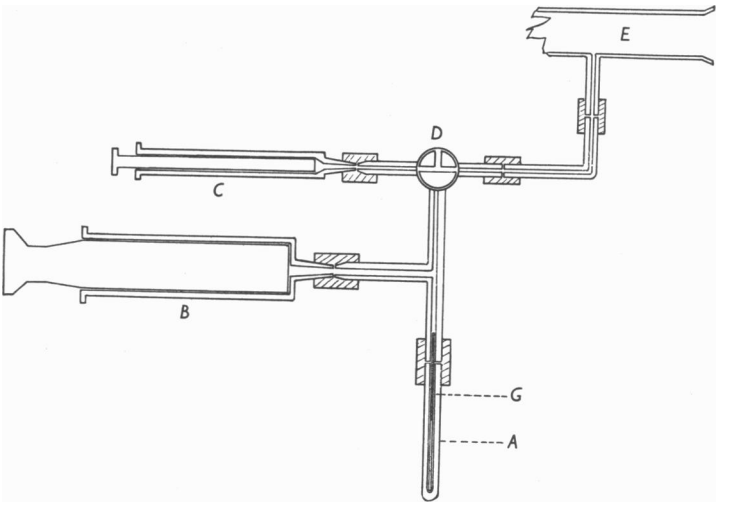

Fig. 1. Apparatus for administration of phosgene. Phosgene is admitted to the bronchial cannula (*E*), which is of wide-bore glass tubing, through the capillary glass inlet connected to the 3-way tap *D*. The small syringe *C* is filled from the larger one *B* as required and this is itself filled when the capsule of liquid phosgene *G* is broken by leverage of *A*, a sealed glass capillary tube just wide enough to admit the capsule. Except for the rubber tubing covering the glass-to-glass connexions, the apparatus is made entirely of glass. When low concentrations of gas are required the syringe *B* is partially filled with air before the capsule is exploded.

The procedure adopted was as follows. A small volume (0·05–0·2 ml.) of pure gas, or of gas mixed with air in known proportions, was injected into the airway during the short pause preceding inspiration so that the succeeding flow of air would wash it into the lungs. The injections were repeated until the required dose of gas had been given, the syringe being re-charged when necessary.

Each injection of gas was necessarily diluted by the volume of air entering the lungs at the succeeding inspiration, but this volume was measured on the spirometer tracing, and therefore the concentration as well as the total dose inhaled could be calculated. Owing to the powerful bronchoconstrictor action of phosgene, the tidal air volume was reduced during the inhalation so that the gas entered the lungs at successively higher concentrations. In some cases the increase was 4- or 5-fold with the tidal air being reduced to as little as 20% of its initial value. Since our object was to ensure that a given quantity of gas was inhaled the rise in concentration that occurred could not be avoided without prolonging the gassing over too long a period to be practicable.

In the majority of experiments the doses employed were between 6 and 20 mg. given at initial concentrations of 0·6 to 2 mg./l. of air (calculated by reference to tidal air volume). Doses of 44 and 54 mg. were tested in two experiments. These were given in concentrations of 10 mg./l. of air.

RESULTS

Conditions for the assessment of experimental oedema. In some of the early experiments carried out according to techniques similar to those used by Daly *et al.* (1946) we found, as had they, that water losses from the system occurred in the respiratory chamber as the result of evaporation from the visceral pleura of the lungs and exposed surfaces of blood. Such losses were sufficiently large to produce a haemoconcentration which masked to some extent the haemoconcentration associated with pulmonary oedema.

In later experiments, however, the modified method already described (Hebb & Nimmo-Smith, 1946) was used and such water losses were then prevented or were too small to alter the haemoglobin concentration significantly. Under these conditions the rate at which oedema developed in a given lung was followed by means of measurements of the haemoglobin (expressed as haem iron) in blood samples taken during the course of perfusion. The total volume of water lost from the blood (with or without other plasma constituents) could be calculated with an error of about $\pm 2\%$. Since the volume of blood in relation to 1 g. of lung tissue was 5–8 ml. this error when expressed in terms of the percentage change in wet weight of tissue was between 10 and 16%. In practice it was found that when the water uptake of the tissue was estimated to be 10% or more of its initial weight the presence of alveolar exudate was always demonstrable histologically.

With the modified technique the later preparations showed a general improvement in that spontaneous oedema was less frequent during the first 4–6 hr. of perfusion. Longer experimental periods were often required, however, and the occurrence of oedema in the control lungs remained a troublesome feature of the experiments. Thus out of twenty-one experiments there were only nine in which no significant extravascular loss of fluid in the controls occurred (4–9 hr. of perfusion). In the others, losses equivalent to an increase in wet weight of tissue of 0·2–1·5 g./g. tissue were found.

The effect of gassing in producing oedema was therefore only clearly evident in the nine experiments in which the controls remained in good condition. In these the gassed lungs showed an increase in wet weight, due to extravascular fluid loss, of 0·3–2·8 g./g. tissue. In nine of the other experiments the figures for the gassed lungs were 0·3–3·5 g., increases which were 1·5 to 20 times those found in corresponding controls. In three experiments only were there no significant differences between the gassed and control lungs. In these three experiments any effects which might have been produced by gassing were overshadowed by gross pathological changes associated with massive haemorrhage into the alveoli and around the arteries and bronchi. This had occurred apparently as the result of obstruction to the circulation since fine fibrin clots were found to be present in various parts of the perfusion apparatus when this was subsequently examined.

In this connexion it may be noted that in our experience there was always haemorrhage of this kind, though not so massive, in all experiments in which there was spontaneous oedema, and it is possible that obstruction to the circulation was a factor contributing to uncontrolled oedema in all cases. In such experiments histological examination showed that the changes found in the control lungs were present in the test lungs as well. The differences were that in the gassed lungs oedema was generalized, while in the control lungs it had a patchy distribution and was often confined to one lobe or part of a lobe; and that peri-bronchial haemorrhage when present was more severe in the gassed lungs. Bronchial desquamation (described also by Daly *et al.*) was also present in gassed lungs which had been perfused for at least 2 hr. after gassing, making its appearance first in the smallest bronchioles and affecting the larger airways later.

It thus appeared from these results that the inhalation of phosgene could cause in isolated perfused lung tissue damage which led to pulmonary oedema; but under the conditions of test obtaining most frequently this was superimposed on an existing damage which could by itself cause pulmonary oedema, although this had a more restricted distribution.

Potassium

A rise in the plasma K above the control values occurred as an early and constant response to the inhalation of phosgene. Typical responses to a large and to a relatively small dose are shown in Fig. 2.

The plasma K normally tends to fall during the first 2 hr. of perfusion (Hebb & Nimmo-Smith, 1946) owing to the transfer to the lungs of an excess which is initially present in the circulation. Part of this is derived from the tissues during bleeding; but the greater part represents a loss from the lungs themselves which occurs while the circulation is stopped during the preparations for perfusion. In some experiments gassing was carried out before all of this excess had disappeared and in these the actual increase in plasma K produced by phosgene was not large (see Fig. 3). Nevertheless, the effect was the same in respect of the differences between the gassed and control lung curves.

Apart from the immediate change in the plasma K level an approximate estimate of the effect produced could be obtained in another way. In Table 1 the amounts of K lost and gained by each lung per unit weight of tissue have been calculated for the whole perfusion period. We have already shown that if there were no experimental interference the values for the lungs should be equal. Thus the differences found can be ascribed to phosgene.

It is probable that the actual differences were in fact much larger than the values obtained by the calculations used to construct Table 1, since these were based on the loss and gain of K from the plasma only. Thus a similar calculation

based on the whole blood values obtained in Exp. C showed that the uptake of K by the control lung was 8·9 mg./100 g. tissue and the loss from the gassed lung 10·3 mg./100 g. lung tissue, giving a difference of 19·2 mg., approximately 90% larger than the value shown in the table. Unfortunately, in other experiments, the whole blood K was only estimated occasionally for control purposes and so a similar calculation cannot be applied to them.

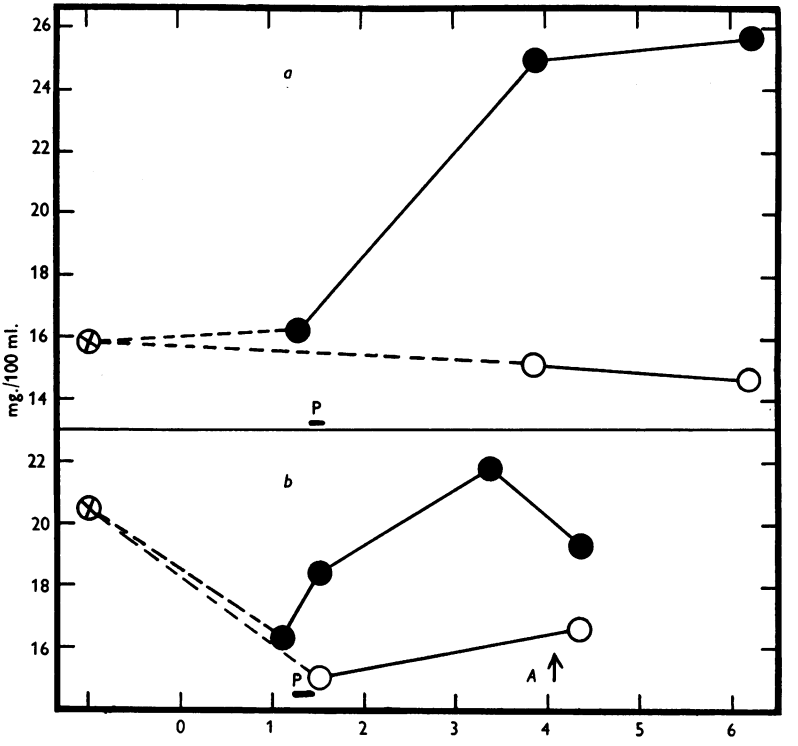

Fig. 2. Plasma K values in control (—○—○—) and gassed (—●—●—) lungs for two experiments. Ordinate: mg. K/100 ml. plasma. Abscissa: hours of perfusion. The initial values for each curve are for the unperfused blood which was collected 30 min. before perfusion started. *a*, 54 mg. phosgene into left lung 1 hr. 25 min. (P) after beginning perfusion; *b*, 13·2 mg. phosgene into left lung 1 hr. 14 min. (P) after beginning perfusion. At *A* injection of 10 μg. adrenaline into each lung circuit.

The rise in plasma K which typically occurred was not so rapid as that produced by adrenaline in experiments already described; nor did it subside so quickly. Usually after reaching its peak, the concentration remained at or near the same value for several hours, although in some experiments (such as that shown in Fig. 2*b*) it fell off gradually.

Control analyses showed, as we have already indicated, that the increase in plasma K was accompanied by a parallel increase in whole blood K. The K_i/K_0

ratio of the erythrocytes was usually of the order of 1·1 (in one experiment only it was 1·6), and it remained nearly constant except for a slight reduction in the presence of severe haemolysis. The error introduced by haemolysis in the

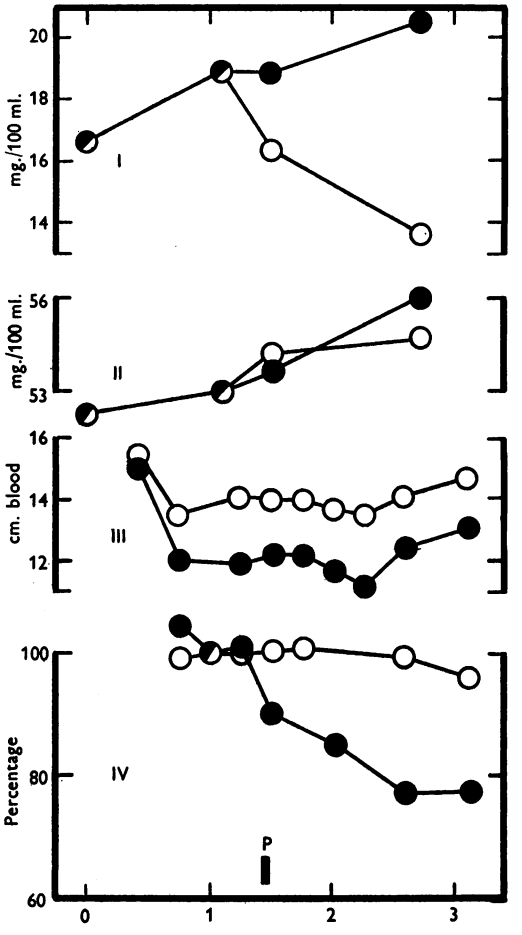

Fig. 3. Values for plasma K (I), blood haem Fe (II), pulmonary arterial pressure (III) and tidal air (IV) for control (—○—○—) and gassed (—●—●—) lungs of one experiment. Abscissa: hours of perfusion. 12·5 mg. phosgene (P) given 1 hr. 25 min. after beginning perfusion. Cross-circulation of the two lungs was maintained for the first 1 hr. 9 min. of perfusion; after that the circulations were separated as in other experiments.

The tidal air values are expressed as a percentage of the volumes obtaining for each lung at the beginning of perfusion.

estimation of the plasma K could, however, never have been more than a few per cent; nor could the exchanges of K between the erythrocytes and plasma have significantly affected the result except, as already indicated, to lead to an underestimate of the amounts exchanged between tissue and blood.

The rise in circulating K was not correlated with broncho- or pulmonary vasomotor responses to phosgene. Bronchoconstriction due to phosgene was of variable intensity and the reductions in tidal air observed ranged from 10 to 80%. On calculating the total K released into the plasma per 100 g. of lung tissue this value was also found to vary widely (between 4 and 35 mg.). This variation could not, however, be related to the variation in the intensity of the tidal air response. Similarly, it was independent of changes in blood pressure, since the release of large amounts of potassium into the circulation occurred in experiments in which no significant changes in pressure were produced as well as in those in which there had been a rise in pressure. There was, therefore, no evidence to suggest that the effect was due to ischaemia. This had been regarded as a possible cause since when the circulation is at a standstill the lungs do lose potassium (cf. Hebb & Nimmo-Smith (1946)).

From the evidence obtained it was most probable that the magnitude of the rise in plasma K depended upon the mass of tissue damaged by phosgene, since there was a rough proportionality between dose of phosgene and amount of K given up per unit of tissue (see Table 1).

TABLE 1. Gain and loss of K by control and phosgene-poisoned perfused lungs

Exp.	Perfusion time	Phosgene (dose in mg.)	Change in K (mg./100 g. tissue)		
			Control	Gassed*	Difference
A	7 hr. 53 min.	44	+ 9·3	−33·9	43·2
B	6 hr. 10 min.	54	+ 3·9	−47·4	51·3
C	4 hr. 20 min.	12·5	+ 5·7	− 5·1	10·8
D	4 hr. 21 min.	13·2	+15·2	+ 6·5	8·7

+ =uptake by tissue; − =loss; values calculated from the plasma K concentration.
* Phosgene administered during second hour of perfusion in each experiment.

It might also be noted that the larger the increase in circulating potassium the longer was the rise maintained (compare Fig. 2*a*,*b*). From this, too, it appeared that the amount of K given up was an index of the quantity of tissue damaged, since evidence was found that tissue not directly exposed to the gas was able to take up some of the excess liberated. This was shown in several experiments, one of which is illustrated in Fig. 4, in which a cross-circulation was established between the lungs during gassing and for a short time thereafter. From Fig. 4 it may be seen that after separation of the two circuits a larger amount of the excess liberated by phosgene disappeared from the control than from the test system as perfusion proceeded. From this it would appear that the effect of the gas was exerted directly on the tissue and was not dependent upon humoral transmission.

The rise in the plasma K was an early effect which had generally reached a maximum before there was any sign of the pulmonary oedema to be observed 1–3 hr. after gassing. If it was due to tissue damage of a non-specific character

it might be expected that a similar rise in plasma K would also occur as a preliminary to oedema in the control lungs. This was not found to be the case,

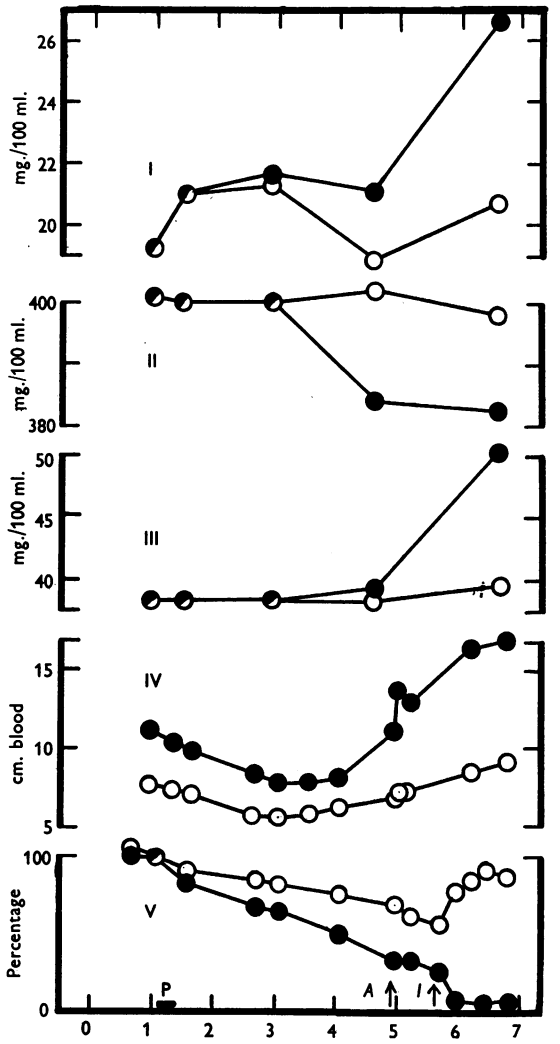

Fig. 4. Values for plasma K (I), plasma Cl (II), blood haem Fe (III), pulmonary arterial pressure (IV) and tidal air (V—percentage of initial values) for two lungs which were cross-circulated before and during gassing. The circulations were separated again 1½ hr. after beginning perfusion. Phosgene (13·2 mg.) was administered at 1 hr. 2 min. Control lung, —○—○—; test lung, —●—●—. At *A* injection of 1 μg. adrenaline into both circulations. At *I* inflation of each lung by positive pressure.

however, and the experiment of Fig. 2*a* may be cited as an example. In this experiment oedema developed in the control lung as a terminal event, and the wet weight increase at the end of the experiment was found to be 0·29 g./g.

but the K remained at low value. In the test lung where a similar change began much earlier the corresponding figure was 3·6 g./g. Analogous results were obtained in other experiments as well. The terminal increases in plasma K of Figs. 2*b* and 4 were due to injection of adrenaline and/or lung inflation (Hebb & Nimmo-Smith, 1946).

The fact that spontaneous oedema was not signalled by a rise in plasma K may not specifically differentiate it from phosgene-induced oedema. It was suggested earlier that stoppage of circulation in parts of the lungs might be a contributing factor to uncontrolled oedema; and if so a localized loss of potassium from the ischaemic tissue should follow. Such an effect might then be marked by the acceptance of excess potassium by the relatively larger bulk of tissue with a normal circulation. This suggestion cannot be regarded as more than speculative, since there is no certainty that spontaneous oedema originated in this way. Nevertheless, in one or two experiments in which there was sufficiently serious interference to the circulation to produce massive haemorrhage, the potassium in the blood remained at the high levels initially obtaining in lungs perfused in this way. In view of these considerations it may then be that the measurable rise in blood potassium and the more generalized distribution of alveolar exudate give a common indication that phosgene poisoning resulted in damaging a large proportion of the tissue, and that the same effect could be produced if in spontaneous oedema the same proportion of tissue were involved.

Chloride and water

Except for quantitative differences the water and chloride changes associated with the onset and development of pulmonary oedema were similar for both gassed and control lungs. The description which follows therefore refers to oedema under both conditions.

Changes in circulating Cl and water of the perfused dog lungs were carefully studied by Daly *et al.* (1946), who found that the combined loss of water and Cl from the blood was a certain indication of pulmonary oedema. In their experiments the event was preceded by a loss of water alone as shown by an initial increase in the concentration of both Cl and haemoglobin. It seemed probable that such water losses occurred as the result of evaporation, and this supposition was confirmed in those of our experiments in which we were successful in preventing such losses.

In these experiments there was no initial loss of water; the migration of water out of the blood was always accompanied by Cl; and the combined uptake of water and Cl by the tissue was indicative of an oedematous change which was progressive and gained momentum as it proceeded. Fig. 4 shows the change in haemoglobin and Cl in an experiment in which there were no measurable evaporation losses. In the experiment of Fig. 3, on the other hand, water losses due to this cause were equivalent to 2·5% of the blood volume in each system.

Another finding of the earlier investigation was that with the development of pulmonary oedema the ratio of Cl to protein gradually fell so that Cl loss apparently preceded that of protein. After perfusion periods of 5–7½ hr. the ratio was reduced by 5–34% (outside limits). It was suggested that this was the result of a progressive increase in capillary permeability. For this view there was the further evidence that oedema fluid collected from the lungs at the end of an experiment had a Cl content which was higher and a protein content which was lower than the corresponding values in the terminal samples of plasma.

From a further examination of the changes in blood and plasma Cl there is evidence to indicate that there was another explanation for these results, namely that the fall in the ratio of Cl to protein was due to contamination of the plasma samples by haemolysis. The evidence was as follows.

In experiments in which there had been no losses of water by evaporation it was observed that coincident with the onset of haemoconcentration the plasma Cl, as well as the whole blood Cl, fell. The fall in whole blood Cl was to be expected since the cell concentration of the ion was usually less than one-half its concentration in the plasma, and the diminution of the volume of plasma relative to the cell volume would therefore have had that effect. On the other hand, the fall in plasma Cl was both unexpected and improbable since it indicated that Cl was entering the tissues at a concentration higher than that existing in the plasma. It had been observed, however, that there was a considerable degree of haemolysis in the centrifuged blood samples taken during the onset and progress of pulmonary oedema; this would by itself account for a reduction of the plasma Cl values owing to the lower concentration of Cl in the erythrocytes. Our suspicion that this was the cause of the fall in plasma Cl was borne out by evidence obtained in two experiments in which we estimated the amount of haemoglobin present in some of the plasma samples used for analysis.

In the experiment shown in Fig. 4 plasma obtained by centrifugation of the terminal blood samples was found to contain haem Fe equivalent in the case of the test lung to 7·3 ml. corpuscles/100 ml. plasma and for the control lung 1·7 ml. corpuscles/100 ml. plasma. Before the onset of haemoconcentration the whole blood Cl was 330 mg., plasma Cl was 400 mg./100 ml., and the red cell volume 33% .The cell Cl was thus 188 mg./100 ml. packed corpuscles. From these values it could be calculated that with the amount of haemolysis which occurred the dilution of the plasma in respect of Cl would be such that the contaminated samples would contain about 383 mg. in the case of the gassed lung and 395 mg. in the case of the control. The corresponding values obtained by analysis were in fact 382 and 398 mg. respectively which was a good enough agreement to indicate that the fall in plasma Cl which had been observed could be wholly accounted for in this way.

Further evidence that the fall in plasma Cl was due to haemolysis was provided by the finding that the fall in whole blood Cl could be wholly accounted for as the result of haemoconcentration and was not as large as would be expected if in addition to an increase in the percentage red cell volume the concentration of Cl in the plasma had also been reduced. Thus in one experiment in which the initial plasma Cl was 402, the whole blood Cl 306 and (by calculation) the corpuscular Cl 179 mg./100 ml. there was an increase in percentage red cell volume from 43 to 52·8 in the terminal sample. If there had been no change in corpuscular and plasma concentrations of Cl in the interval between the two samples, then in the second one the whole blood Cl should have been 293·5 mg./100 ml. By analysis it was found to be 294 mg./100 ml. On the other hand, the plasma Cl in the second sample was found to be 370 mg./100 ml. and if this were used as a basis for calculation then the whole blood Cl should have been much lower, or it must be assumed that the cell chloride had increased from 179 to 225 mg./100 ml., a result which is extremely unlikely.

Haemolysis would not only have led to a fall in plasma Cl; it would also have caused an apparent decrease in the ratio of plasma Cl to protein, partly owing to the relatively high protein content of the corpuscles. In the experiment which has just been considered, if it were assumed that the protein of the cells was 30% and that of the plasma 6·5% (values taken from results of Daly *et al.* 1946) then the degree of haemolysis present in the terminal plasma sample taken from the gassed lung circuit would account for an increase in plasma protein of about 1·8%. Thus, while the ratio of Cl to protein would have been 400 : 6500 (0·062) in the unhaemolysed sample it would be 382 : 8300 (0·046) in the haemolysed sample. This would represent a diminution in the value of 25% which is nearly equivalent to the largest reduction observed in the earlier investigation.

The evidence which has been given in respect of the change in whole blood chloride, and its close correspondence to the change expected to occur on the basis of the increase in percentage red cell volume, indicated that the haemolysis observed was an *in vitro* and not an *in vivo* change, which probably occurred during the centrifugation of the blood. In agreement with this we found, in one experiment in which we were able to analyse three successive samples of oedema fluid, that the Cl concentration in the three samples was 397 ± 1 mg./100 ml. and that in the initial plasma sample it had also been 397 mg./100 ml.; but that after the onset of oedema, the plasma values were 382 and later 370 mg./100 ml. The explanation of this finding appeared to be once again that owing to haemolysis the terminal plasma values were lower than those which really obtained in the circulation. In the same experiment it was found that the values for K concentration of the plasma and oedema fluid over the same experimental period were in agreement within the limits of experimental error.

This was to be expected in view of the nearness of the corpuscular K_i/K_0 ratio to unity and that haemolysis could consequently not produce any large changes in the plasma concentration of this ion. From these observations we concluded that the lack of correspondence between the composition of the oedema fluid and coincident plasma samples, in respect of Cl and protein, which had been observed earlier, could be wholly accounted for as the result of haemolysis produced in the preparation of the plasma samples. Because haemolysis was always present to some degree in the terminal plasma samples obtained in the investigation made by Daly *et al.*, this seemed to invalidate the previous evidence that Cl loss preceded protein loss from the blood. In fact, if haemolysis reached proportions equivalent to that found in some of our experiments then the order of change in the ratio Cl to protein found earlier becomes insignificant, and it would appear that the losses of protein and Cl were initiated at the same time and proceeded at the same rate.

On our interpretation the true significance of the plasma Cl changes which were found to be associated with the onset of oedema was the indication which they gave of an increased fragility of the corpuscles. In our experience the consistent occurrence of significant haemolysis in the separated plasma samples was as good a sign as any of the onset of pulmonary oedema. It was equally true that when this sign was absent, oedema was not found on other criteria. We can offer no explanation of this phenomenon, and while various causes might be suggested we have at present no evidence on which to base our speculations.

DISCUSSION

The genesis of pulmonary oedema in the phosgene-poisoned lungs presents a problem of special interest. In view of the low pulmonary arterial pressures (6–12 cm. water) which normally obtain before the onset of oedema this cannot be thought to be circulatory in origin. Similarly, at such low pressures, the colloid osmotic pressure of the blood should effectively counter any tendency to oedema unless, through damage, the capillaries suddenly become relatively more permeable to protein. Thus the onset of oedema is probably associated with the escape of protein from the circulation, and it would be expected that protein, chloride and water would diffuse outwards at their existing plasma concentrations. The evidence we have discussed is compatible with this view and there is no longer any reason to assume that the loss of water and crystalloids must necessarily precede that of protein.

Besides the occurrence of oedema the only other evidence of an effect of phosgene on the capillaries is the increase in capillary blood volume of the gassed lungs. Thus Daly *et al.* (1946) found that at the termination of an experiment the amount of blood which could be expressed from the vessels by positive pressure inflation is larger for gassed than for control lungs. This effect, which we find can be demonstrated for any pair of lungs perfused for 1 hr. or longer

after one has been gassed, is probably the result not only of an increased capillary blood volume but possibly also of a tendency for other intrapulmonary vessels of gassed lungs to be compressed under positive pressure inflation. The hyperaemia and congestion can be seen from direct inspection, and the lung haemoglobin figures of Daly *et al.* (1946) suggest that more blood is retained by control than by gassed lungs after drainage by inflation. An increased tendency for the capillaries of gassed lungs to collapse during positive inflation cannot be invoked in explanation of this phenomenon, since it is fairly certain that both normal unperfused lungs and also lungs perfused at constant input pressure have their capillaries emptied by a few mm. pressure (Daly, 1949). It seems that an explanation may exist in the response of other intrapulmonary (and possibly also of extrapulmonary) vessels to positive pressure inflation.

We have not sufficient evidence to assess the significance of the loss in tissue K which precedes the onset of pulmonary oedema. It seems probable that it is released as a result of damage to tissue directly exposed to the gas; the largest bulk of this is alveolar. It might be suggested, therefore, that the rise in blood K which follows exposure to phosgene is an early signal of the change in this tissue which is later responsible for its increased permeability and hence for the occurrence of pulmonary oedema.

The observation described in our previous paper that the perfused lungs normally take up K during the first 1 or 2 hr. of perfusion is at variance with the results of Wood & Moe (1942), who found that over the same period the whole blood and serum K of the blood-perfused dog lungs remains constant. The difference may be, however, because Wood & Moe employed positive pressure ventilation in their experiments (personal communication from Wood), whereas we have used only negative pressure ventilation. This suggestion is made on the grounds of our previous experiments in which it was found that a single inflation of the lungs by positive pressure may temporarily reverse the fall in plasma K which otherwise occurs.

SUMMARY

1. In isolated blood-perfused lungs of dogs the inhalation of phosgene may initiate oedema or augment oedema arising spontaneously in the course of perfusion.

2. The onset of oedema, with a latent period of 1 or 2 hr. after poisoning, is preceded by a marked increase in blood and plasma K above the control values. The increase occurs slowly and is maintained for long periods. This change is not observed as a preliminary to 'spontaneous' oedema.

3. Evidence is given that in the genesis of pulmonary oedema, water and Cl leave the plasma together at the existing plasma concentration of Cl.

4. Increased fragility of the red blood corpuscles in the perfusing blood is associated with the onset and progress of pulmonary oedema from phosgene and other causes. Evidence is given that the resultant haemolysis occurring during the preparation of plasma samples may be large enough to produce errors in the estimation of plasma Cl and protein.

These experiments were part of a programme of research carried out in this laboratory on behalf of the Ministry of Supply to whom we are indebted for permission to publish the results. We would also like to thank Prof. I. de Burgh Daly and Dr P. Eggleton for their interest and encouragement, and for valuable advice in the course of investigation. Dr O. A. Trowell gave us welcome assistance in examining histological material, and we should like to thank him and Miss Jean Banister who assisted in some of the experiments.

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